# Modeling and experimental validation of radiation - Cell interaction in radiotherapy by photon activation of gold nanoparticles

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# Summary

- Context
- State of the art of gold nanoparticle photoactivation therapy
- Physics and Monte-Carlo simulation
- First results of simulation with Penelope code
- Conclusion and prospect

# Context

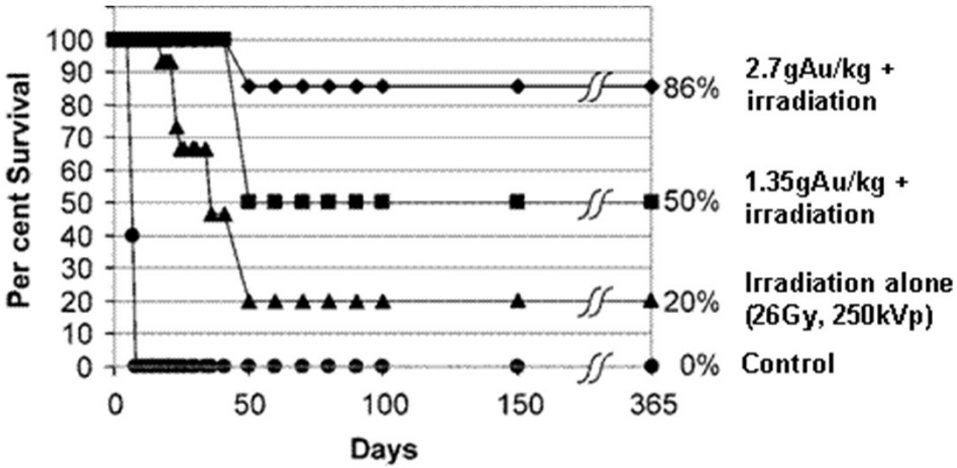
- **Current limitations of radiotherapy:**
  - The tolerance of healthy tissues
  - The inability of irradiation techniques to treat diffused cancers (ex: Glioblastomas).

- **Concept of heavy element enhanced radiotherapy :**
  - Irradiation with a low energy X-ray beam (50 - 150 keV) in the presence of high Z elements.
  - Enhancement of the dose effect in the tumor loaded with high Z element and creation of complex damages at the cellular level.

- **Goals:**
  - Understand physical phenomena connected to these enhancement effects using Monte Carlo simulation and experimental measurements (provided by ESRF).
  - Focus here on gold nanoparticles (GNP).
  - Use of different physical parameters as emitted electrons spectra and Dose Enhancement Factor (DEF).

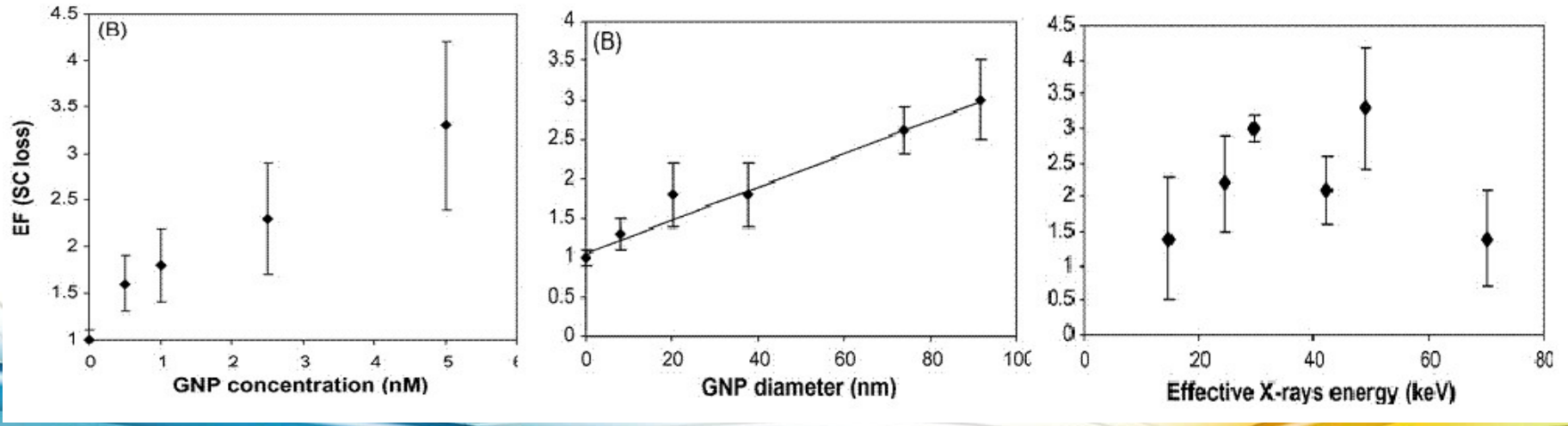
# State of the art : GNP photoactivation therapy

- **Study of Hainfeld et al. (Phys. Med. Biol (2004)) :**
  - Very good survival response, up to enhancement of 4, by treating cancerous mice combining injection of GNP of 1.9nm and irradiation with a RX tube at 250kVp.




- **Hainfeld (Phys. Med. Biol (2010)):**
  - New *in vivo* results using the same technique but with synchrotron beam at 68 and 157 keV.

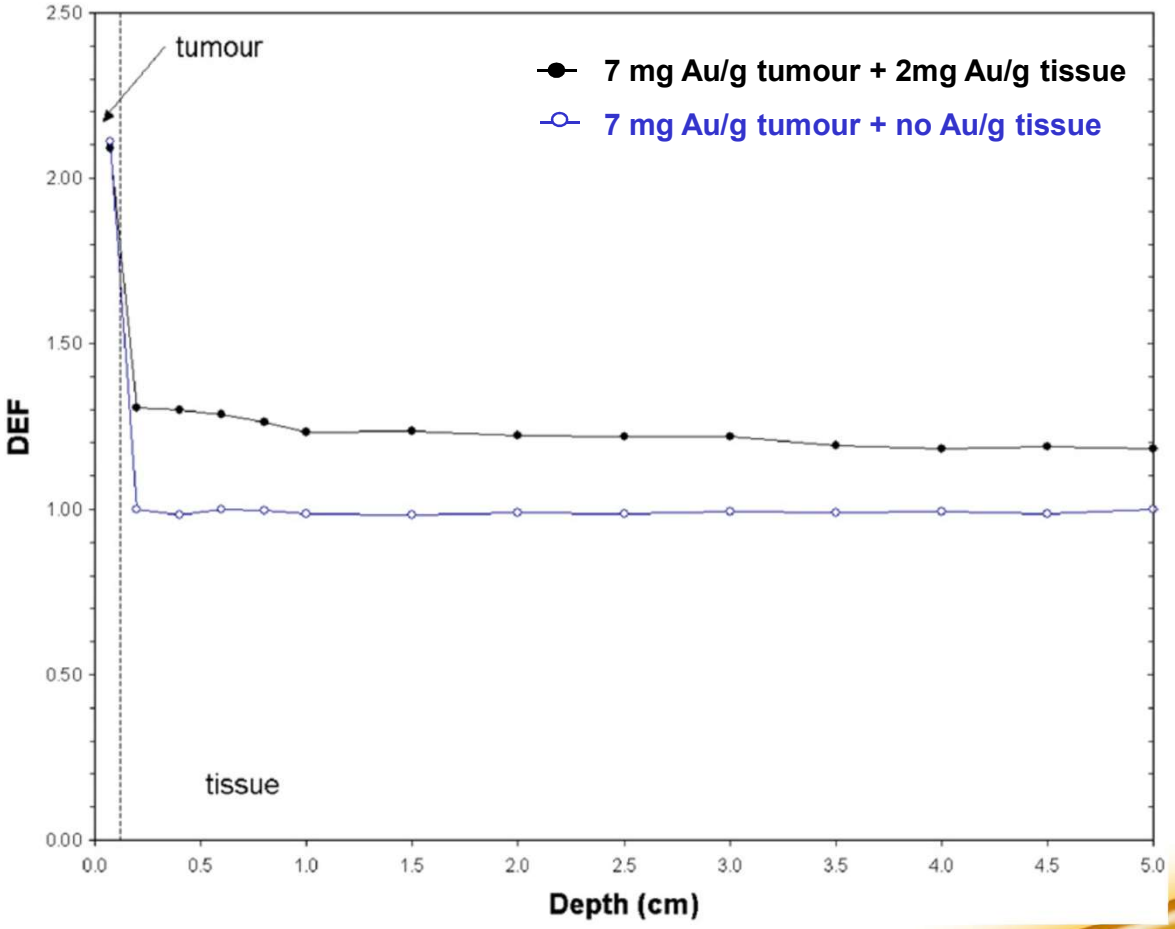
- **Radiosensitization experiments with GNP (E. Brun et al. 2009):**



# State of the art : Monte Carlo simulation with GNP

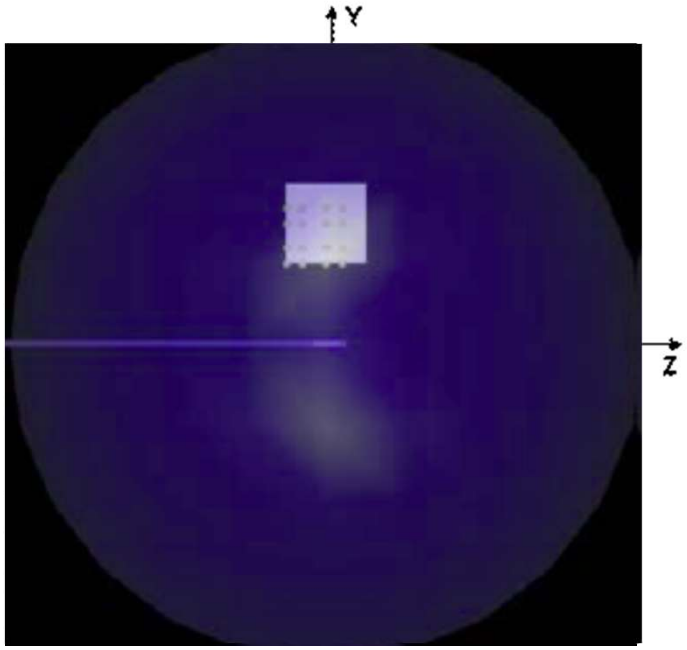
- **Cho et al. (Phys. Med. Biol. (2005)):**
  - Attempt to reproduce Hainfeld's results.
  - Model representing a tumor embedded with a gold-water mixture.
  - Obtained a DEF of 2.1 into the tumor.

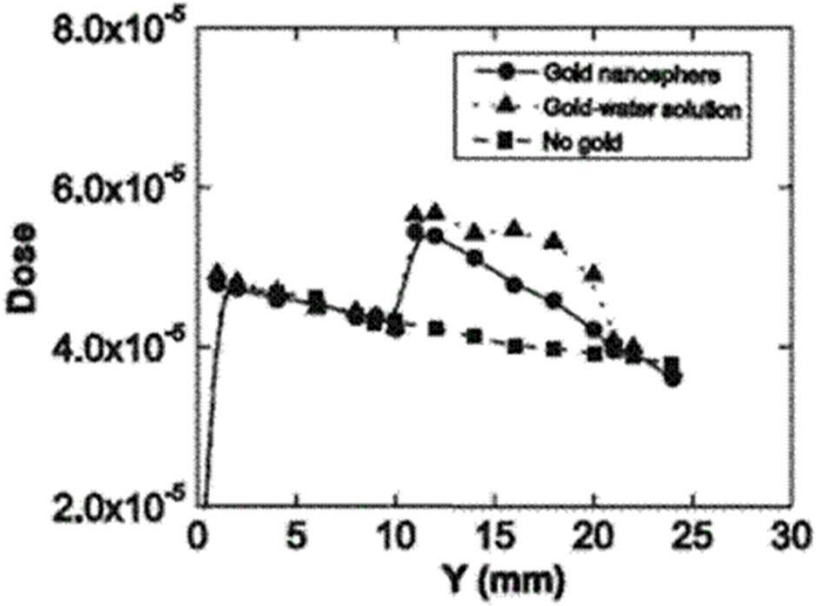
→ **Need a model which takes into account the distribution of GNP and microdosimetry.**



# State of the art : Monte Carlo simulation with GNP

- **Zhang et al. (Biomed Microdevices (2009)):**
  - Comparison of calculated macroscopic dose with two different model:
    - Homogeneous gold-water mixture (Cho's 2005 method).
    - Structure with gold nanoparticles.



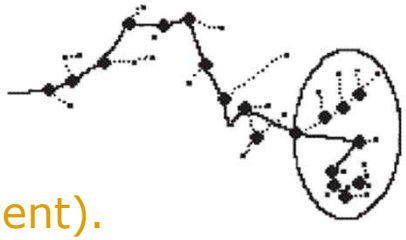




  - The homogeneous gold-water model overestimates the dose until 16% in the target volume. → Confirm the need of modelling the nanostructures.

# State of the art : Monte Carlo - track structure code

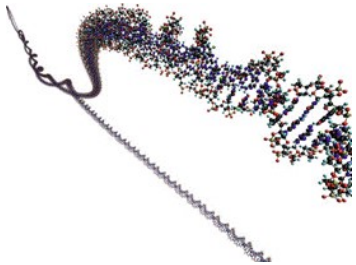
- **Previous macroscopic studies show the importance of:**
  - Modelling geometries and calculating doses at a micro and nano level.
  - Finding parameters more relevant than physical dose to describe the phenomena.

- **Monte Carlo codes called "track structure" can be used to simulate very precisely electron and photon transport. Main codes:**



  - Penelope: adapted for clinical radiation dosimetry and transport description of low energy X-Ray and electrons.
  - EGS: adapted for clinical radiation dosimetry.
  - MCNPx: not precise to model relaxation cascades (in development).
  - G4: developed for high energy physics, now extended to all radiation physics (project : G4DNA).

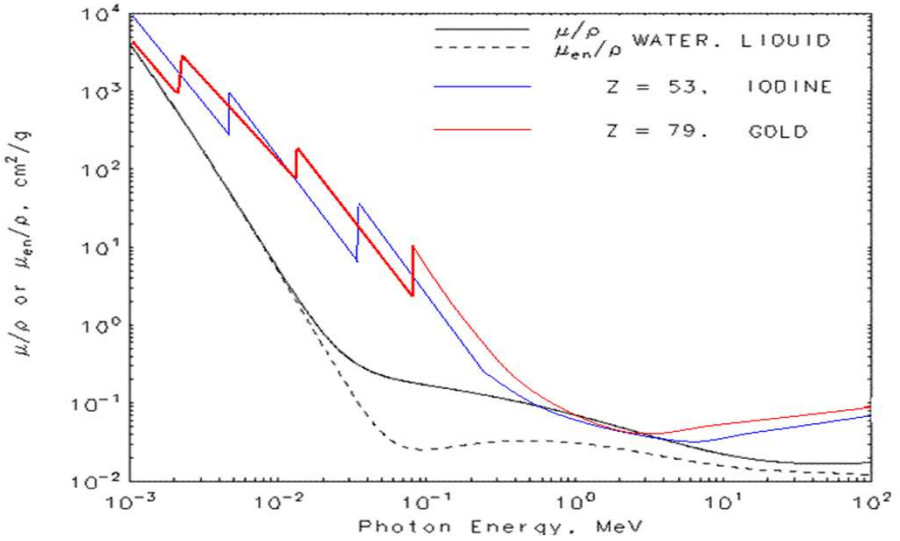
- **Some are used to describe interaction of particles with DNA :**



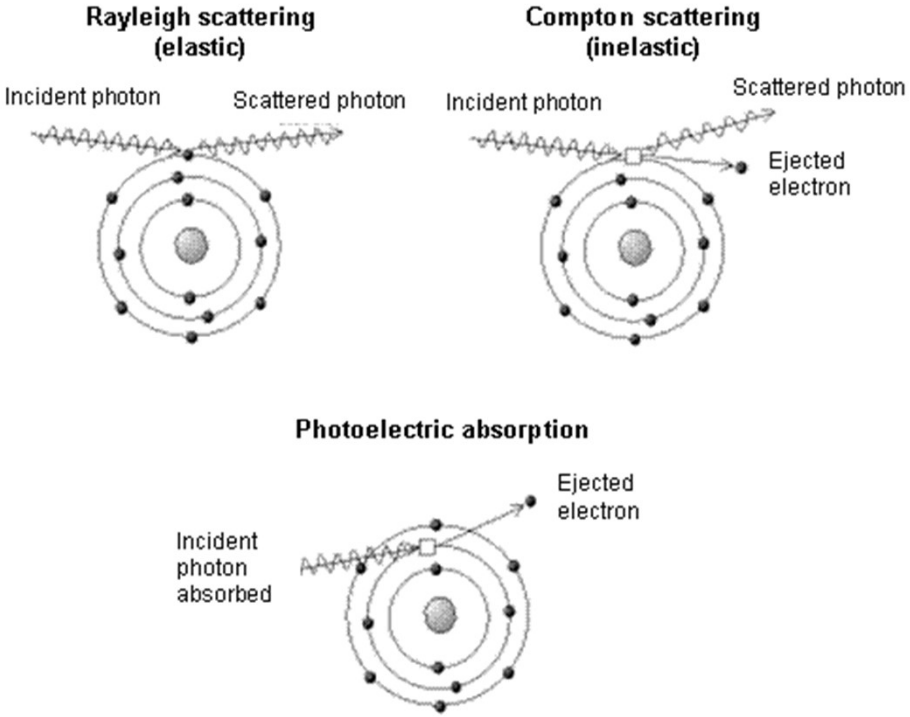
  - Ftacnikova et al. (Radiation Protection Dosimetry (2000))
  - Terrissol et al. (Int. J. Radiat. Biol. (2008))
  - Nikjoo et al. (Radiation Protection Dosimetry (2006))

# Physics and Monte Carlo simulation

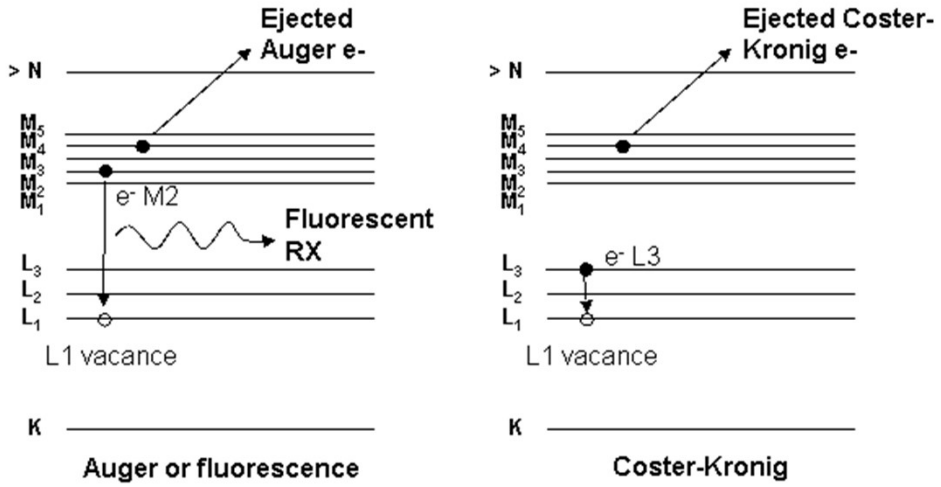
- **Monte Carlo method :**
  - Allow to follow the particles transport in matter according to random processes determined with interaction probabilities.



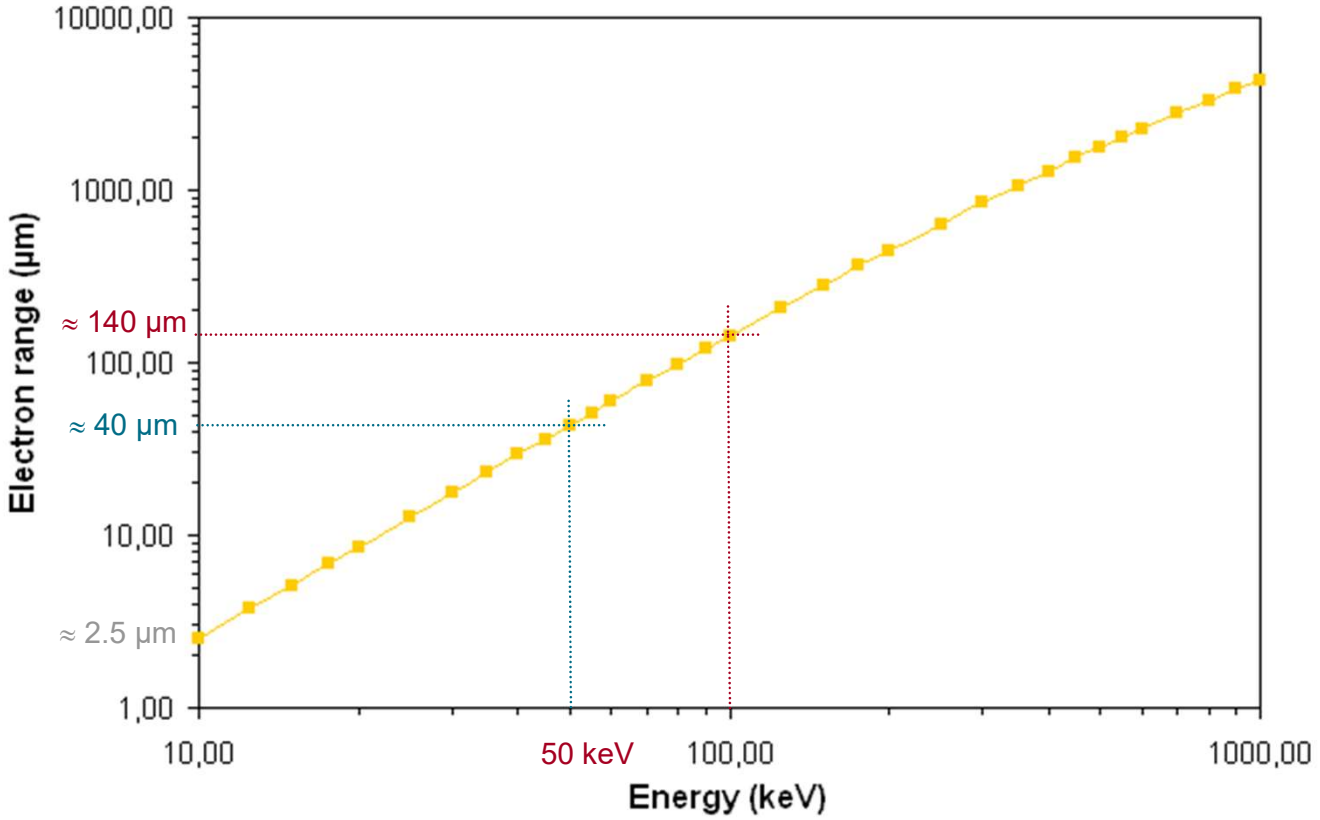

- **Photon interaction :**




- **Atomic relaxation :**



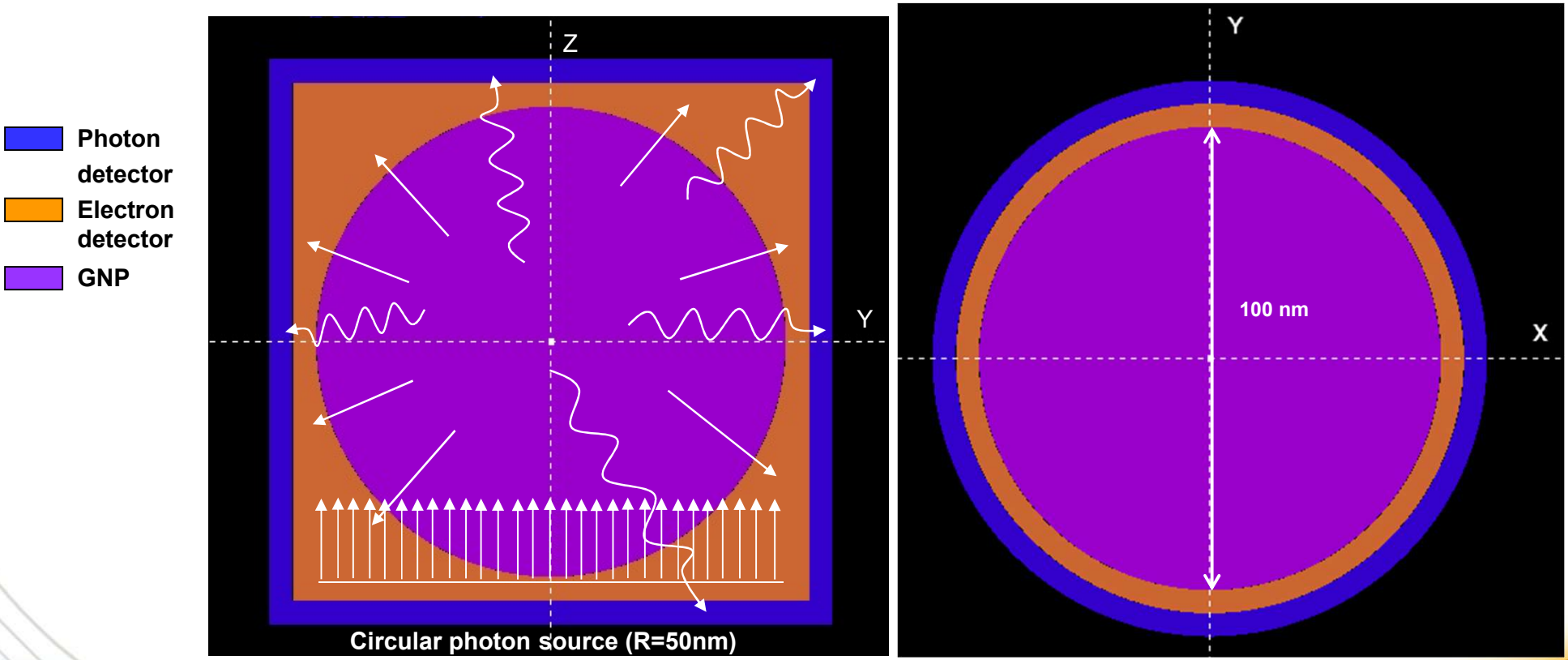
- **Electron range in water, ESTAR (NIST databases):**



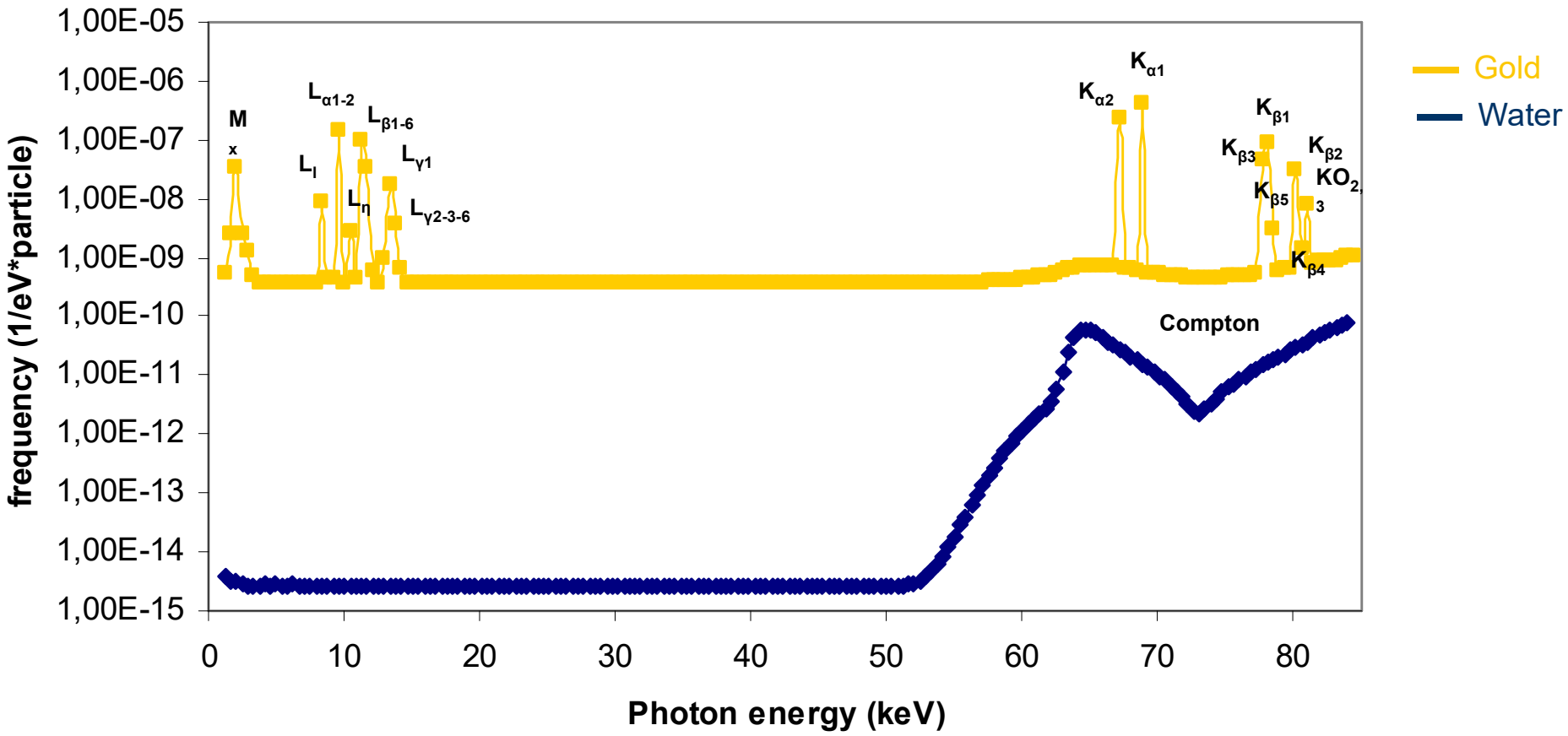

- Range of 10 keV electron ≈ 2.5 µm in water, nucleus scale.
- Range of 50 keV electron ≈ 40 µm in water, cellular scale.
- Range of 100 keV electron ≈ 140 µm in water, few cells.

# Penelope code

- **Gold nanoparticle geometry, spectrum study:**
  - sphere of 100 nm diameter, full of water or gold.
  - Detectors are virtual tools which quantify the spectrum of outgoing particles.

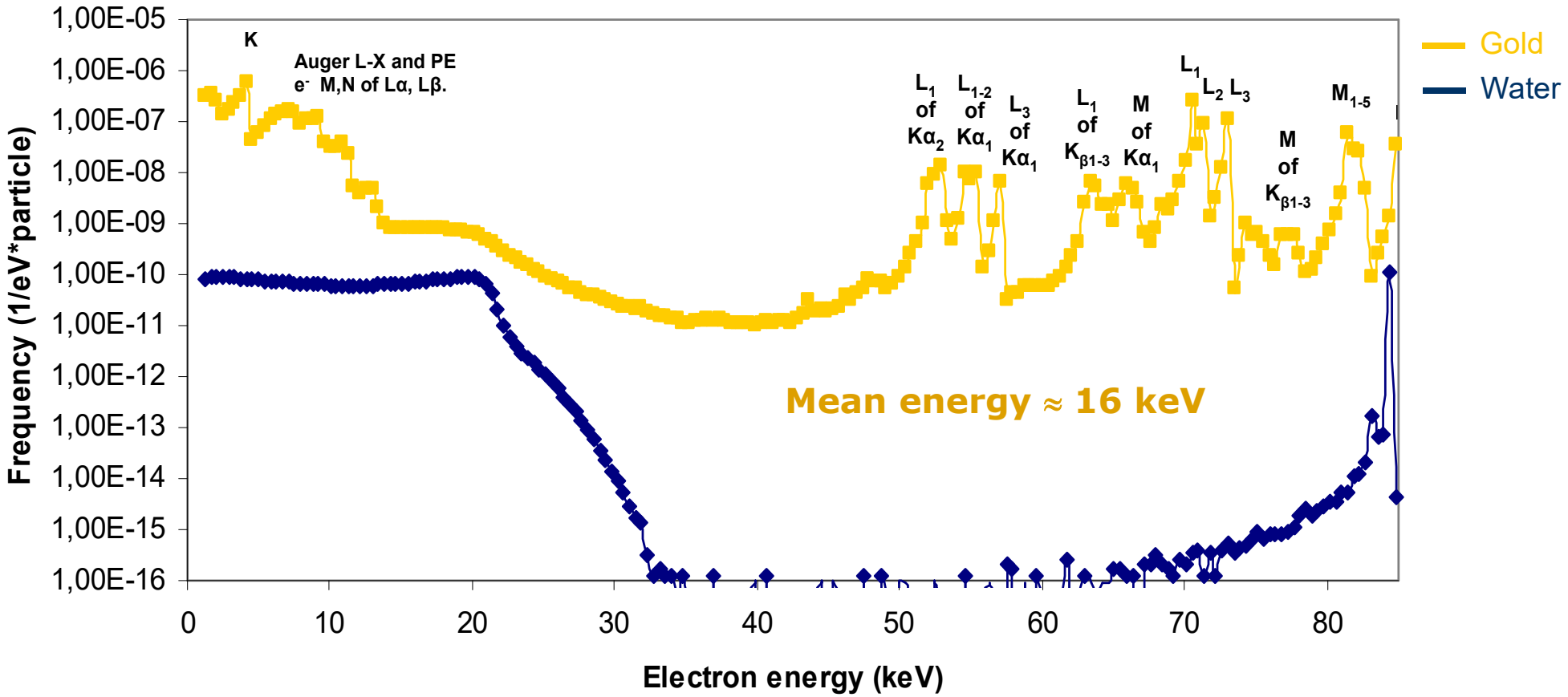


# Outgoing photon spectrum for 85 keV monoenergetic beam



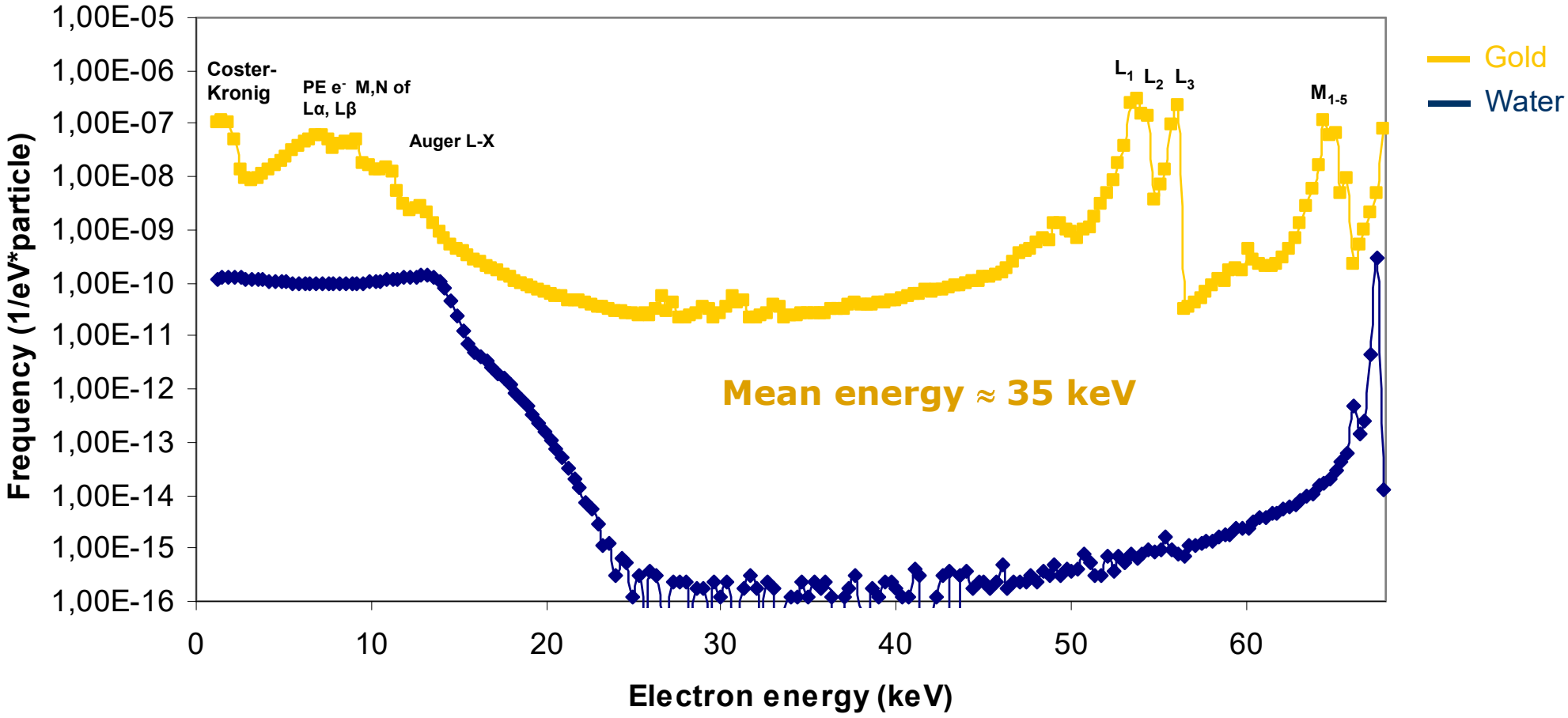

→ **Fluorescence relaxation well described in Penelope.**

# Electron spectrum for 85 keV monoenergetic beam



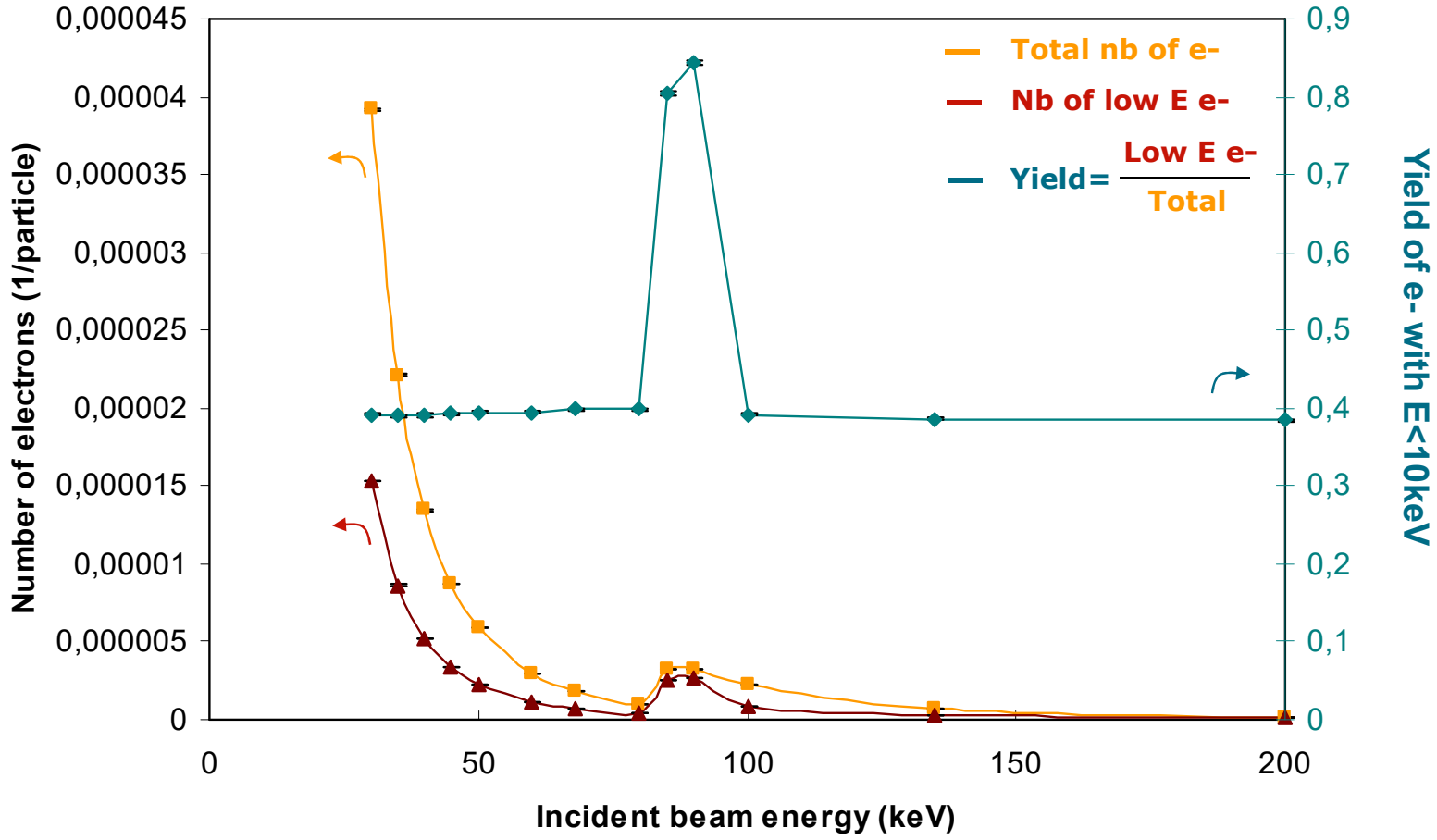

→ **Relaxation cascade and X-ray interaction with shell and sub-shell well described in Penelope.**

# Electron spectrum for 68 keV monoenergetic beam



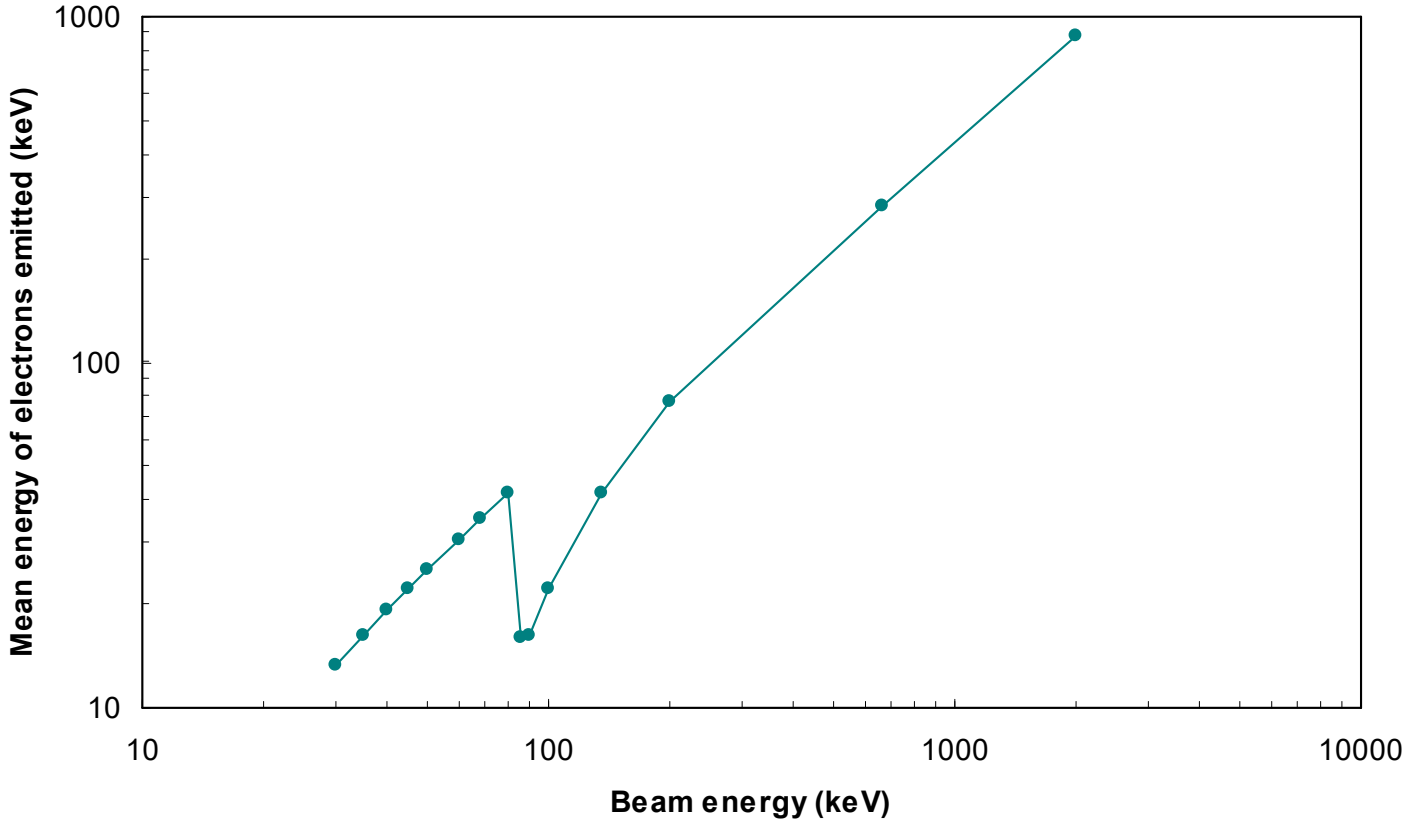

→ **Modification of the spectra before and after the K-edge: influence on the mean energy and range of electrons created from the GNP.**

# Study of total electrons emitted and the yield of low energy electrons (< 10 keV) produced in GNP as a function of beam energy




→ **Strong enhancement of the yield of low energy electron (range of few µm) after the K-edge due to the photoelectric absorption.**

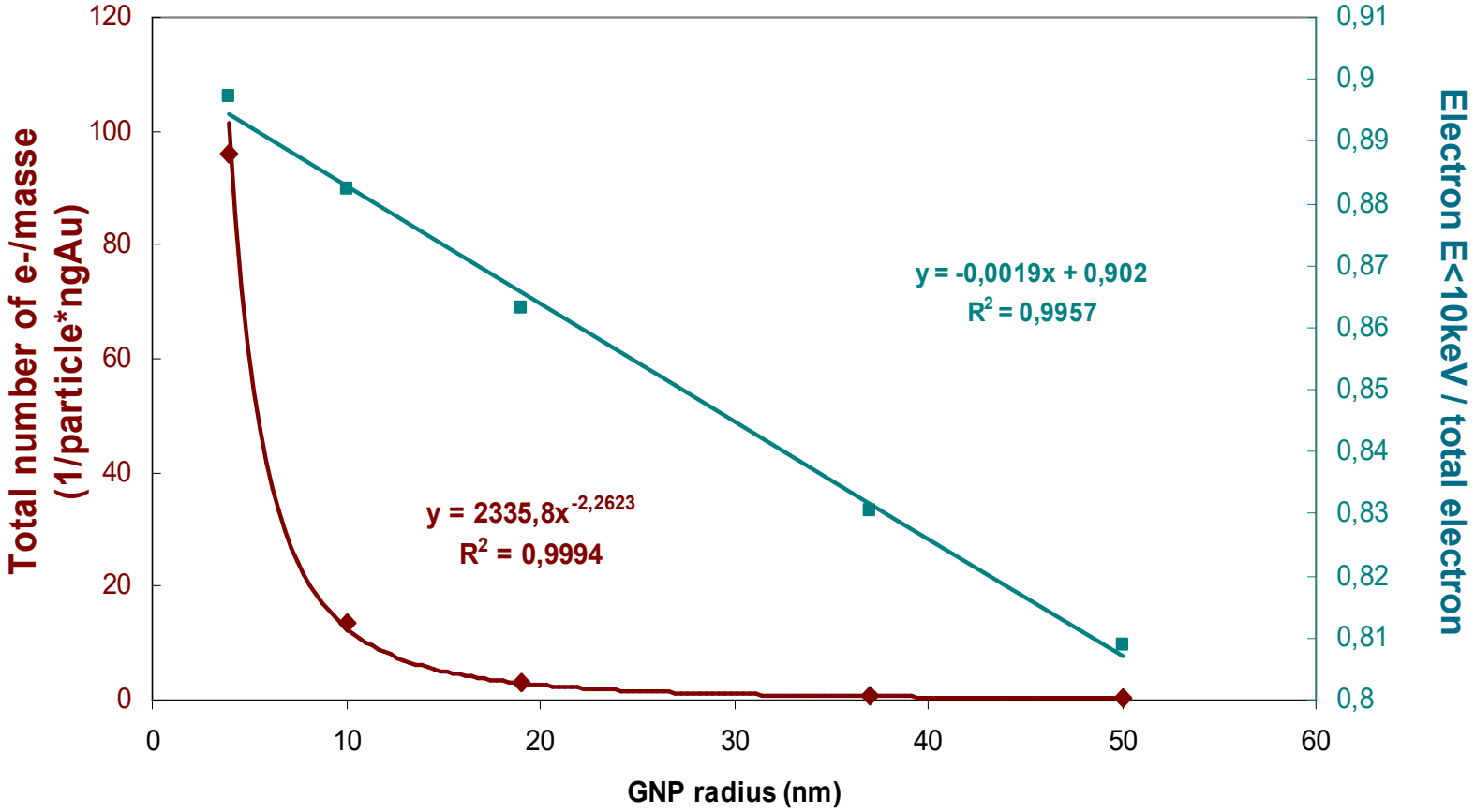
# Mean energy of electrons emitted from the GNP as a function of incident beam energy




→ **Mean energy of electrons emitted from the GNP increases with the incident beam energy and falls down after the K-edge.**

→ **Optimization of beam energy as a function of the GNP targeting.**

# Study of total electrons emitted and the yield of low energy electrons (<10keV) produced in GNP as a function of GNP radius

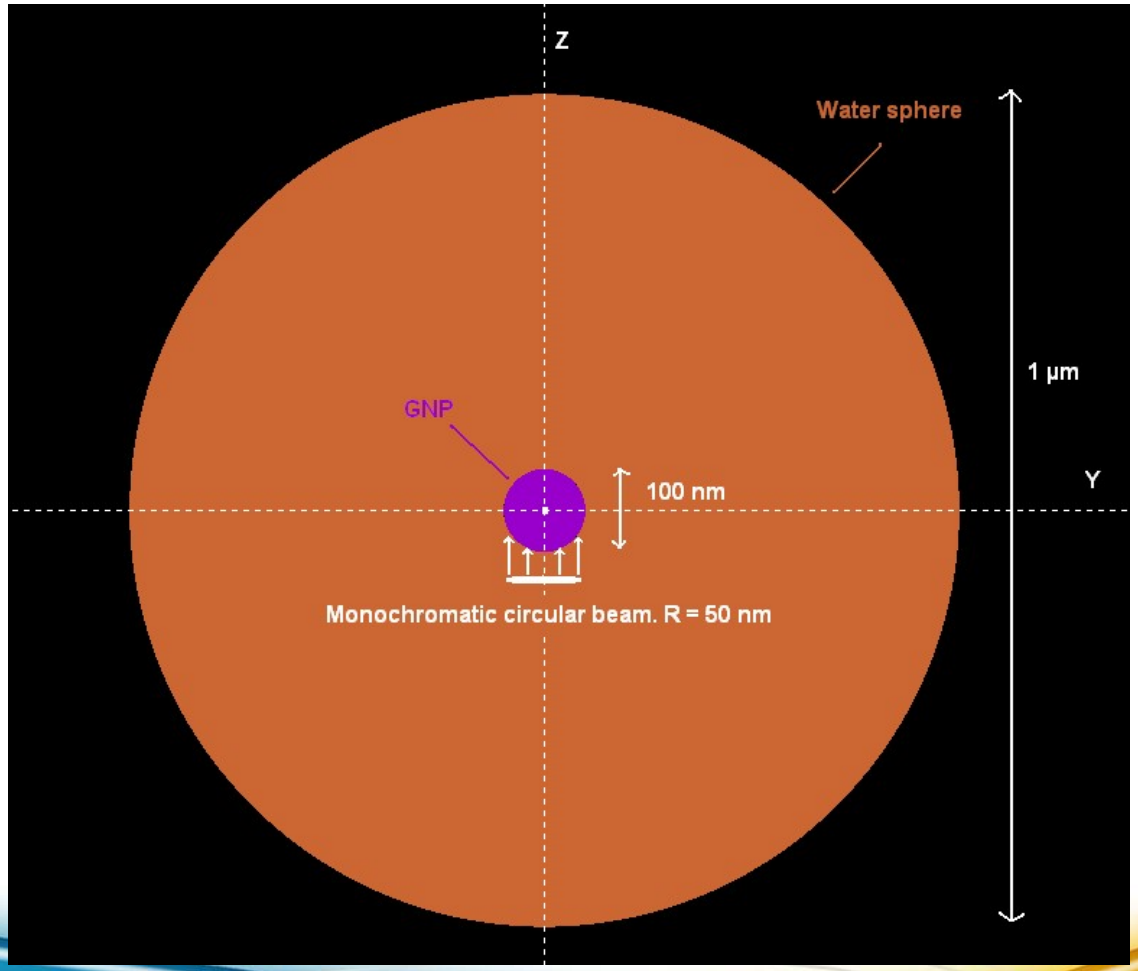



→ **Total number of electrons relative to the mass of gold seems to decrease as a $1/x^2$ tendency with the GNP radius.**

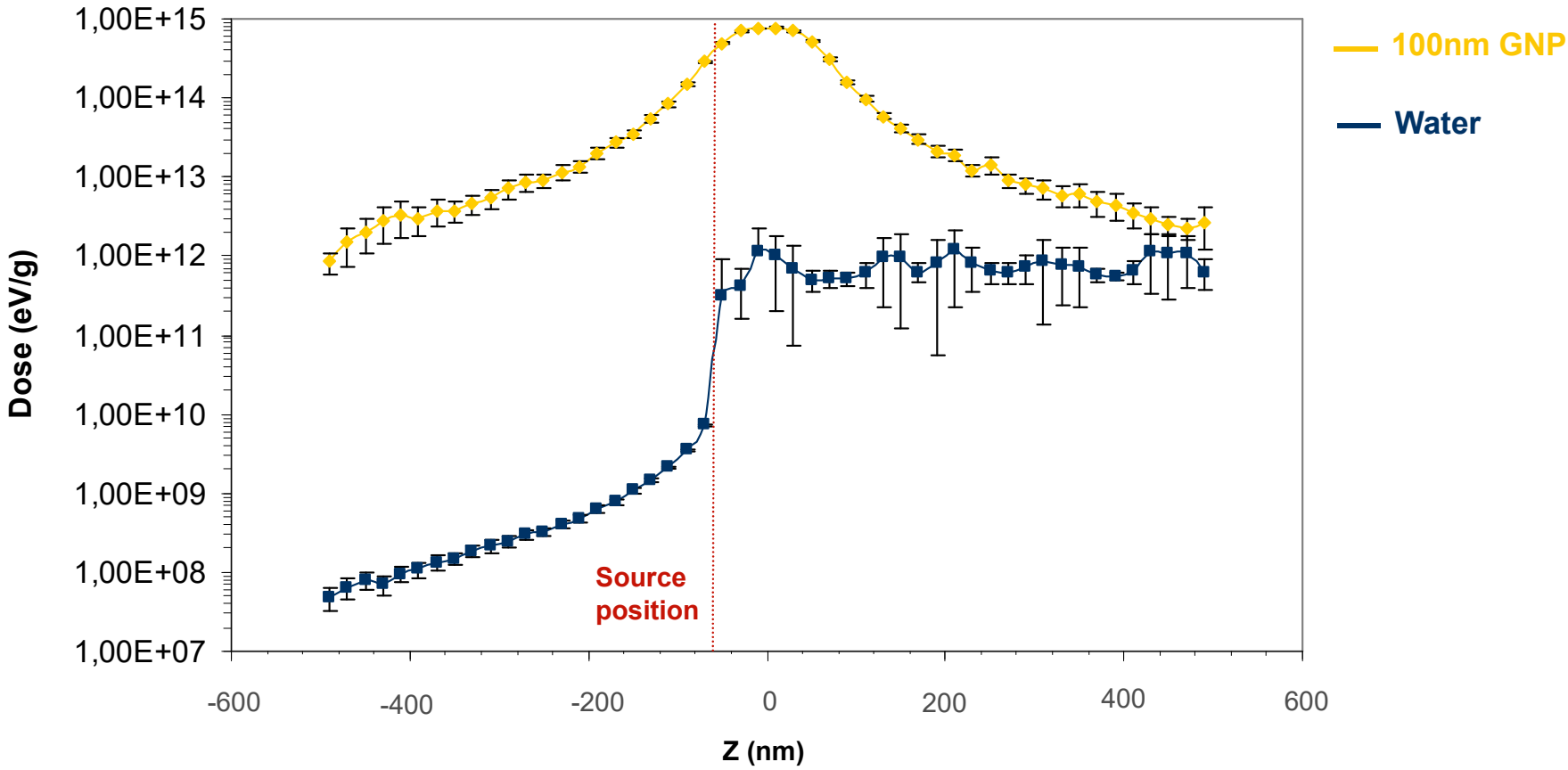
→ **Yield of electrons lower than 10 keV decreases linearly with the GNP radius.**

# Study of microdosimetry around the GNP

- **Dose study :**
  - Geometry: spherical GNP of 100 nm diameter in a water sphere of 1 µm.
  - Study of the deposited dose due to the GNP in the water sphere.



# Dose profile on the Z axis for a 85keV monochromatic beam

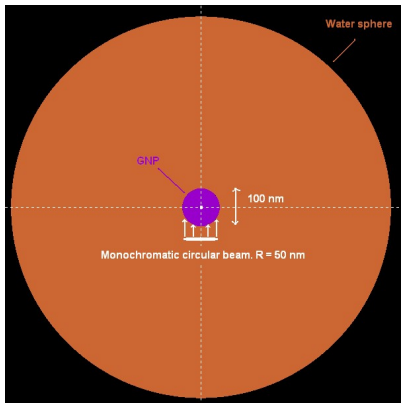


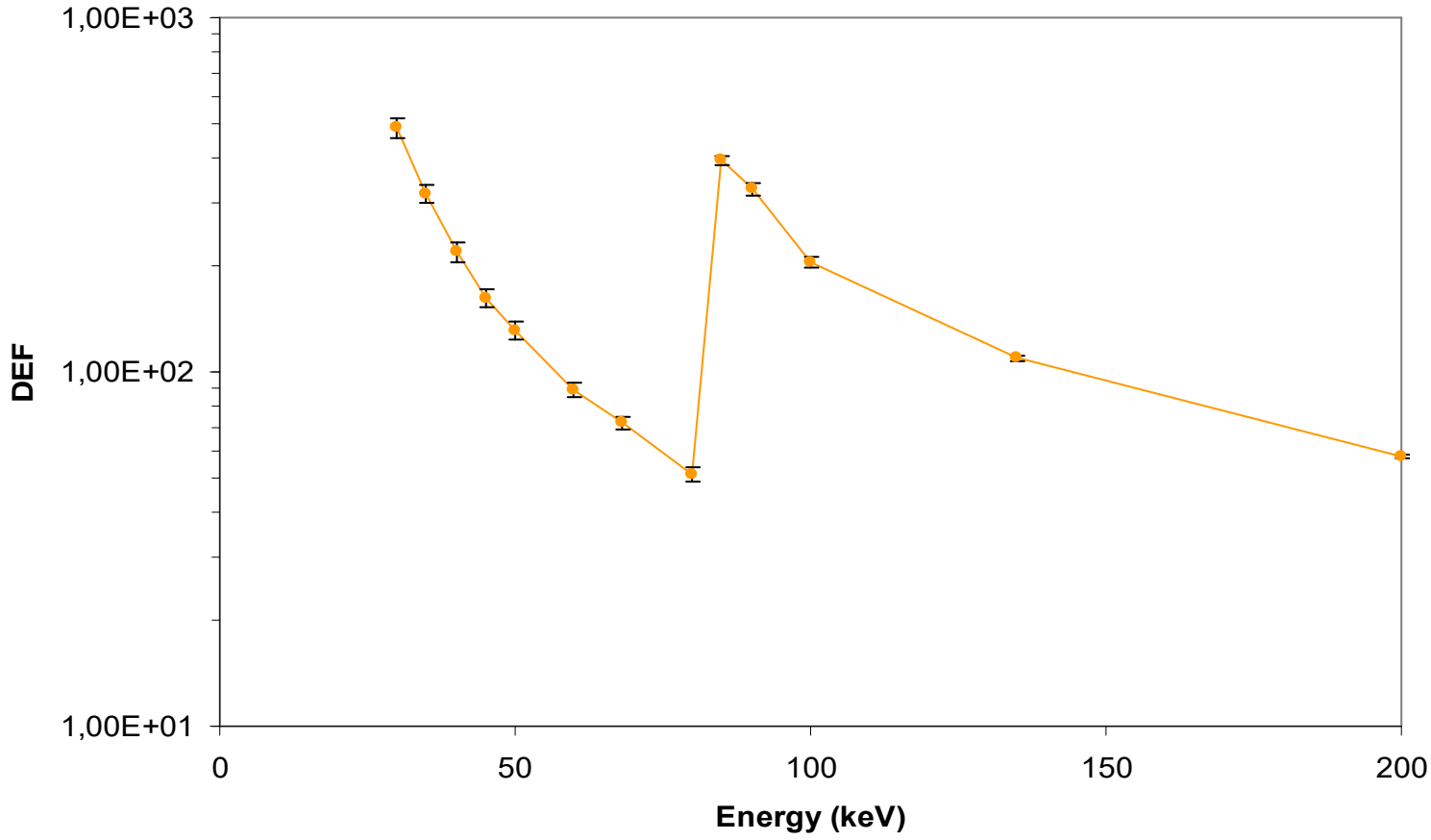

→ **Deposited dose due to the GNP is dominated by the low energy electrons produced.**

→ **Quasi-isotropic diffusion of dose around the GNP at a µm scale.**

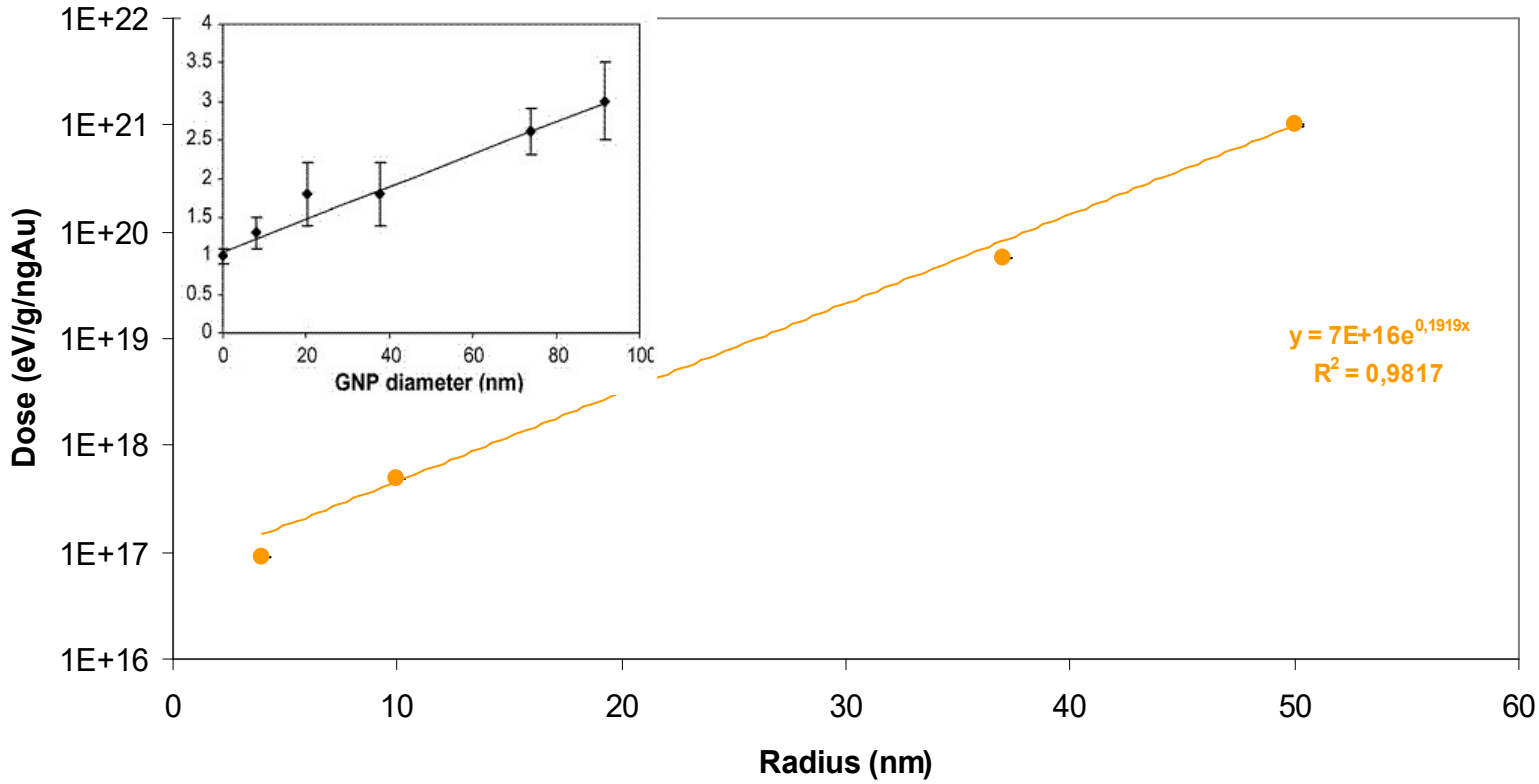
# DEF calculated as a function of beam energy with a 100 nm GNP

$$\text{Dose Enhancement Factor} = \frac{\text{Mean dose in the water sphere with GNP}}{\text{Mean dose in the water sphere without GNP}}$$



# Mean dose calculated as a function of GNP radius for a 85 keV monochromatic beam




→ **Deposited dose in the 1 µm water sphere due to the GNP increases with the radius as a exponential tendency.**

→ **The increase of electron production for small GNP does not influence the dose at a µm scale.**

# Conclusion and prospect

- **Conclusion :**
  - Photoactivation radiotherapy with GNP induces complex dose effects at a cellular level and requires more precise study of the local effect of GNP.
  - This study aims understanding physical phenomena correlated to these local effects.
  - The characterization of GNP in terms of particles created and local physical dose deposited are described according to the beam energy and the radius of spherical GNP.
- **Prospect :**
  - Study these local characteristics in a more realistic geometry.
  - Experimental measurements planed to study the dependency with beam energy.
  - Study different geometries of GNP.
  - The challenge is to find a relevant parameter to see correlation between physical data and biological results.